Allergy Abstracts

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Announcement

Allergy Abstracts has been published since 1936 by members of the Allergy Division of The Jewish Hospital of Brooklyn. The Editorial Board is comprised of former residents of this department who contribute their services.

Allergy Abstracts selects and abstracts those articles in the literature which may be of clinical or theoretical interest to workers in the field of allergy. Each abstract represents a summary of the author's findings and views, and its inclusion in Allergy Abstracts does not imply approval of its contents by the Editor.—*The Editors.*

Asthma and Hay Fever

Delirium and Coma Precipitated by Oxygen in Bronchial Asthma Complicated by Respiratory Acidosis. Beale, H. D., Schiller, I. W., Halperin, M. H., Franklin, W., and Lowell, F. C.: New England J. Med. **244**: 710, 1951.

A 53-year-old man with a history of bronchial asthma for fourteen months became irrational, stuporous, or comatose on two occasions during severe attacks after he had received oxygen therapy by nasal catheter at a flow of 6 liters per minute for a few hours. When the oxygen was discontinued the patient awakened, even though he became cyanotic. Administration of oxygen during the attack produced a marked depression of ventilation. Although the minute volume did not change, the rate became more rapid and the tidal air was greatly depressed. There was an increase in carbon dioxide

tension, a fall in arterial pH, and virtually complete saturation of the arterial blood with oxygen. After the patient's condition had improved under treatment with cortisone and the pH and carbon dioxide content of the arterial blood had returned to normal, ventilation and intrapulmonary-gas-mixing studies were within normal limits. At this time inhalation of oxygen no longer caused significant changes in the arterial carbon dioxide tension or pH, even though the arterial oxygen saturation rose to 100 per cent. The possible mechanisms involved in the clinical phenomenon are discussed. The authors believe that carbon dioxide narcosis occurs in the presence of high arterial oxygen saturation in patients with respiratory acidosis. They advise that great caution be exercised in the administration of oxygen to patients who suffer from chronic hypoxemia and carbon dioxide retention. I. Glazer.

Treatment of Eosinophilic Pneumopathy. Report of a Case Treated With ACTH. Vines, R. W., and Clark, D.: New England J. Med. **244**: 826, 1951.

A 41-year-old woman with a history of various allergic manifestations including bronchial asthma developed a nonproductive cough, dyspnea, fever, pulmonary infiltrations, and an increased erythrocyte sedimentation rate. There was no leukocytosis; blood eosinophiles varied from 0 to 14 per cent. Penicillin, Aureomycin, and streptomycin therapy produced no appreciable improvement. The pulmonary infiltrations persisted and became more extensive six weeks later at which time the sputum was loaded with eosinophiles. Repeated therapy with pencillin, Chloromycetin, Aureomycin and sulfadiazine was of no avail. The patient rapidly became more acutely ill and had to be placed in an oxygen tent. Respirations were 40 per minute. She developed a mild leukocytosis and the circulating eosinophile count became 9100 per c.mm. or 35 per cent of the leukocytes. ACTH was administered intramuscularly at the rate of 25 mg. every six hours. After two days, there was considerable improvement and oxygen was discontinued. The patient became afebrile, the blood eosinophiles dropped to 25 per cubic millimeter, lung roentgenograms showed improvement, and the sedimentation rate declined gradually. The dose of ACTH was gradually decreased. When it was discontinued, there was a relapse of symptoms with eosinophilia, pulmonary infiltrations, and increased sedimentation rate. A second course of ACTH in smaller doses caused a remission which lasted for one year. The differential diagnosis is discussed in detail. I. Glazer.

Administration of Cortisone by the Aerosol Method in the Treatment of Bronchial Asthma. Gelfand, M. L.: New England J. Med. **245**: 293, 1951.

Five patients ranging in age from 42 to 65 years, who had had bronchial asthma of the intrinsic or combined type for twenty to twenty-five years, were treated with aerosol cortisone. One cubic centimeter of Cortone, containing 25 mg. cortisone acetate, was diluted in 4 c.c. saline. One cubic centimeter of this solution was nebulized hourly for ten hours daily. No other therapy was given except for occasional small doses of Adrenalin. Four patients responded favorably after the fourth day and all signs of bronchospasm disappeared on the seventh day. The fifth patient, who had marked emphysema and pulmonary fibrosis, failed to respond. Relapses occurred in 3 of the 4 successfully treated patients after the fourth or fifth day following the cessation of therapy. They responded satisfactorily to readministration of the cortisone. At the start of the inhalations, there was an increase

in coughing and hoarseness developed. These symptoms disappeared as the asthma improved. Fifty milligrams of nebulized cortisone daily was apparently the optimal dose for these patients. It is suggested that the direct application of cortisone to the bronchial mucosa acts by interference with the union of antigen and antibody, by inhibition of histamine liberation at the site of the shock organ, or by systemic action following absorption through the mucous membrane. I. Glazer.

Stress Studies in the Eczema-Asthma-Hay-Fever Diathesis. Sternberg, T. H., and Zimmerman, M. C.: Arch. Dermat. & Syph. **65**: 392, 1952.

The alarm reaction response to an injection of epinephrine and an artificially applied stress situation was studied in a group of 27 patients with atopic eczema. Both atopic patients and control subjects responded normally to an injection of epinephrine, as measured by the eosinopenic index, indicating that patients with atopic dermatitis have an intact and properly functioning pituitary and adrenocortical mechanism. Following artificial stress, atopic patients showed an abnormal eosinopenic response. Since the pituitary and adrenal cortex respond normally to exogenous epinephrine, it is inferred that the cause of the abnormal response in these patients lies in the higher brain centers or in the adrenal medulla. This may be the reason why patients with the atopic diathesis can be precipitated into an acute exacerbation by a variety of emotional stimuli. These include all types of physical stress, acute viral and bacterial infections, and specific allergic incidents. These precipitating factors all have a common denominator in that they all initiate the alarm reaction in normal persons. This reaction is nonspecific and the physiologic changes which take place are the same, irrespective of the type of stimulus which triggers the mechanism. C.

Lycopodium Allergy. Salen, E. B.: Acta Allergologica **4**: 308, 1951.

Lycopodium is the name given to the spores of the moss, *Lycopodium clavatum,* which belongs to the fern species. Lycopodium allergy occurs among theater personnel, pharmacists, metal workers using wooden molds treated with lycopodium powder, workers in the fireworks industry, hairdressers using dry shampoo containing lycopodium, and among women using such preparations at home.

An interesting case of lycopodium allergy occurred in a 7-year-old boy who had severe seasonal asthma and rhinitis. Cutaneous testing was essentially negative except for a four-plus positive reaction to lycopodium extract. A positive passive transfer reaction was also obtained. It was found that the child's summer symptoms occurred in a region where lycopodium plants were plentiful at a time when these plants were "blooming." Sensitization evidently had been induced by recurrent visits to this area since early childhood. The spores of lycopodium are smaller than timothy, pollen grains, and approximately the size of birch pollen granules. A positive cutaneous reaction with lycopodium was obtained in 61 cases of rhinitis, with or without asthma. In 34 of these cases, the reactions were of one-plus or plus-minus degree. Completely negative reactions were obtained in many nonallergic and allergic individuals. Provocative exposure tests and histories proved lycopodium to be the etiologic allergen in 27 cases. In many instances, positive passive transfer reactions were obtained. Specific desensitization was successfully carried out in 11 cases. The writer suggests that lycopodium may be a frequent cause of allergic symptoms. H.

Histaminase and the Destruction of Histamine in Asthmatics. Jiménez Diáz, C., Perianes, J., Arjona, E., Lotrente, L., and Aguirre, M.: Rev. clín. españ. **39**: 250, 1950.

Following the administration of histamine, the blood histamine curve was found to be similar in both asthmatics and normal subjects. No increase in the histaminase activity of the plasma was noted in asthmatics. A marked increase in plasma histaminase activity occurs in anaphylactic shock. H.

Basal Metabolism and Bronchial Asthma. Quarles van Ufford, W. J.: Acta Allergologica **4**: 327, 1951.

The literature on the relationship between the thyroid gland and allergic symptoms was reviewed.

Basal metabolic tests were performed on 420 patients with bronchial asthma. Rates between minus 10 and plus 20 were considered normal. Decreased metabolic rates were recorded in 27 (6.3 per cent) cases and increased rates in 114 (26.7 per cent) cases. Decreased rates occurred predominantly in children. Thyroid medication improved the general condition of these patients but had little effect on the asthma. In hyperthyroidism, the author suggests that Adrenalin and potassium iodide be avoided and that therapeutic measures be directed toward the hyperthyroid state. Although the writer considers it unlikely that the thyroid gland exerts any influence on the pathogenesis of bronchial asthma, he feels that thyroid disturbances may influence the course of asthma. H.

Intravenous Injection of ACTH. Hedstrom, V.: Svenska läk.-tidning. **48**: 2809, 1951.

Sixteen patients with bronchial asthma were treated with intravenous injections of ACTH. From 2 to 3 mg. of ACTH diluted in 10 ml. of normal saline was administered 3 times daily. All patients became symptom free in from three to six days. Recurrences occurred in all treated patients within five weeks after discontinuing treatment. No side reactions were noted. H.

Does Desensitization Affect the Adrenals? Dragsted, P. J.: Acta Allergologica **4**: 340, 1951.

Six patients who were receiving specific hyposensitization for hay fever were investigated for the effect of hyposensitization on the activity of the adrenal cortex.

Values obtained for potassium, sodium, chlorine, and protein content of the blood, the eosinophile count, and the excretion of 17-ketosteroids and glucosteroids in the urine failed to reveal any evidence that increased activity of the adrenal cortex occurred during hyposensitization treatment for hay fever. H.

Otorhinology and Ophthalmology

New Concepts in the Use of ACTH in Ophthalmology and Otolaryngology. Bissell, G. W.: Tr. Am. Acad. Ophth. **56**: 450, 1952.

Five hundred seventy-five complete examinations of the upper air passages were made on 60 patients who were undergoing ACTH therapy for various illnesses. Certain uniform changes were noted in all the patients. The nasal mucosa developed a dusky appearance, swelling and discharge were

reduced, and clear mucus covered the mucosa. Nasal crusts and ulcerations disappeared and the lymphoid tissue in the nasopharynx developed an orange-pink hue. Fifteen patients with nasal polyps, who were treated with ACTH, improved within twenty-four hours. There was a rapid loss of nasal edema, decrease in nasal discharge, and within two to three days the polyps either disappeared or were reduced in size. This improvement lasted for not more than six weeks. Topical application of cortisone in the form of sprays or packs was ineffective in the treatment of nasal polyposis. Injection of cortisone into the nasal mucosa in 5 mg. doses resulted in a temporary shrinkage of the membranes. When the dosage was increased to 25 mg. a violent reaction ensued, characterized by flushing of the face, substernal pressure, wheezing, and collapse. Histologic sections of nasal polyps before and after cortisone therapy showed no changes except a slight decrease in edema. It is pointed out that resistance to cortisone is not uncommon. Patients with vasomotor rhinitis and asthma who responded favorably to cortisone and ACTH for two seasons, failed to show improvement in the third year of treatment. Patients who have received cortisone therapy have a resultant adrenal hypoactivity and are therefore not suitable patients for surgery until a recovery period of several weeks has ensued. C.

Bacterial and Cytological Diagnostic Criteria in Nasal and Sinus Disease. Goldman, J. L.: Ann. Otol., Rhin. & Laryng. **61**: 120, 1952.

Microscopic study of spreads of nasal and sinus secretions and cultural study of these secretions can be used as major criteria in differentiating infections from noninfectious disorders of the nose and sinuses. Although allergic and vasomotor rhinitis may exist when eosinophiles do not appear in the nasal secretion, their presence in large numbers strongly suggests an allergic etiology, particularly if no microorganisms are seen in the spread. On the other hand, a large number of white blood cells and microorganisms usually indicate infection. Pneumococci, hemolytic streptococci, *Streptococcus viridans, Staphylococcus aureus A* in large numbers, *Hemophilus influenzae,* and *Klebsiella pneumoniae* are very rarely found in the normal nose and sinus. Hence, isolation of any of these microorganisms from the secretions of the nasal cavity or sinuses strongly suggests the presence of infection. If spreads of the secretion on stained slides show the same microorganisms and large numbers of neutrophiles, the existence of infection is further substantiated. On the other hand, *Staphylococcus albus B,* Neisseria species, diphtheroids, and usually *Staphylococcus albus A, Staphylococcus aureus B, Staphylococcus aureus A,* in small numbers are present in the normal nose and are not associated with infection. Thus, if any of these are cultured from nasal or sinus secretion it is unlikely that infection exists. If spreads of such secretion show no microorganisms and a considerable amount of mucus, then the evidence is strong that the disease is not one of infection. Correlation of findings on the spread and culture permits the establishment of precise diagnostic information. C.

Aural Manifestations of Allergy. Derlacki, E. L.: Ann. Otol., Rhin. & Laryng. **61**: 179, 1952.

The author presents the case histories of therapy-resistant chronic cases of external otitis, of suppurative otitis media, and of secretory otitis media which were found to be allergic in origin and responded to specific allergic management. The examination of aural secretions for eosinophiles is as valuable a diagnostic measure in chronic allergic ear diseases as it is in nasal allergy. C.

Miscellaneous Allergies

Penicillin Allergy. Irving, J. W., Graham, M. J., Jacobson, B. M., and Burrage, W. S.: New England J. Med. **245**: 246, 1951.

A 45-year-old physician with a positive family history and a negative personal history for allergy developed a severe reaction following an intramuscular injection of penicillin. He had handled penicillin for five years and had received 14 daily intramuscular injections of 300,000 units of procaine penicillin for furunculosis. When a new furuncle appeared seven months later an intramuscular injection of 300,000 units of procaine penicillin was given. Within five minutes, there was a generalized tingling sensation, pruritus of the scrotum, flushing of the face, unsteady gait, dyspnea, and a burning sensation of the chest. All these symptoms subsided within five minutes. Three weeks later the patient received another intramuscular injection of 300,000 units of procaine penicillin G. Within thirty seconds, he experienced a generalized tingling and hot sensation, pruritus of the scrotum, dyspnea, weakness, and a cold sweat. Auscultation revealed wheezing and râles. There was a drop in the blood pressure and the radial pulse could not be felt. A gradual improvement followed within fifteen minutes. Several weeks later when procaine penicillin was spilled on a finger abrasion, the area began to itch immediately and became erythematous. Conjunctival injection appeared on the following day. Scratch tests made with penicillin sodium, 1,000 units per ml., and with undiluted procaine penicillin G (containing aluminum monostearate) resulted in very large positive immediate reactions. Scratch and intracutaneous tests with procaine solutions gave negative reactions. Patch tests with aluminum monostearate gave negative reactions. Passive transfer studies yielded positive results in one of three recipients. It is suggested that the shocklike symptoms in this patient were probably the clinical manifestation of an antigen-antibody reaction. I. Glazer.

Egg Allergy in Children. Ratner, B., and Untracht, S.: Am. J. Dis. Child. **63**: 309, 1952.

Three hundred twenty-two supposedly nonallergic children were studied to determine the incidence of clinical and skin sensitivity to egg. One child (0.3 per cent) was found to be clinically sensitive and two others showed one-plus dermal reactions to egg. Ten of 192 of these children also tested with chicken feathers were found to have positive skin reactions to this allergen. Among 500 known allergic children scratch tested with egg, 102 showed positive reactions. Ingestion tests were made on a majority of the reactors and about 20 per cent developed clinical manifestations of sensitivity. Thus, approximately 5 per cent of allergic youngsters were found to have a clinical egg sensitivity. The authors stress the need for more careful evaluation of positive skin reactions to egg and the necessity for correlating these reactions with the patient's clinical history. R. W.

Systemic Sensitivity to Various Mercurial Diuretics. Robbins, M. H.: New York State J. Med. **52**: 593, 1952.

A 57-year-old woman with rheumatic heart disease and cardiac decompensation was treated with the mercurial diuretic, Mercuprocyl, daily for six days with an excellent response. Four hours after the next 2 c.c. intramuscular injection of Mercuprocyl she developed a chill and her temperature rose to 102° F. The temperature returned to normal the next day. Following the next injection of Mercuprocyl, she again developed chills and fever,

severe pains in the back, and then went into shock, from which she rapidly recovered. She required further cardiac therapy and was therefore hospitalized. She was given test doses consisting of 0.05 c.c. of Mercuhydrin several times and on each occasion she developed a febrile response. Thiomerin was then tried in gradually increasing doses. With the last injection of 1.2 c.c., the patient developed nausea, weakness, dizziness, and fever. Since the patient was in desperate need of diuretics, Mercuhydrin was again given and again the patient developed fever, respiratory distress, and shock. Her condition gradually deteriorated and she finally expired fifty-one days after being admitted to the hospital. On post-mortem examination, the kidneys were found to be essentially normal. This patient apparently became sensitive to the entire group of organic mercurial diuretics. B. S.

Purpura Due to Quinidine. Lipson, L.: New York State J. Med. **52**: 586, 1952.

A 75-year-old woman suddenly developed auricular fibrillation. She gave a history of having had a similar episode several years before for which she was treated with quinidine with no untoward reactions. She was given 3 gr. doses of quinidine sulfate and after 9 gr. the fibrillation reverted to a normal rhythm. After 5 doses, epistaxis was noted. The patient had taken 33 gr. during a period of three days before the drug was finally withdrawn. At this time, she had a diffuse purpuric eruption, a large subconjunctival hemorrhage, and bleeding from the mouth. Bleeding began to subside within twelve hours after discontinuing the quinidine. The bleeding time was over fifteen minutes, clotting time, 6.5 minutes, hemoglobin, 60 per cent, red blood cells, 3,510,000, white cells, 3,950 with a normal differential. Platelets could not be seen on the blood smear. Blood was found in the stool and urine. Three days later, the bleeding time was two minutes, the clotting time remained at 6.5 minutes, and platelets were seen on the blood smear. At this time, the patient was feeling well. B. S.

Fatal Acute Iodism After Bronchography. Sumner, J., Lichter, A. I., and Nassau, E.: Thorax **6**: 193, 1951.

The authors report a fatal case of iodism which followed the instillation of 14 c.c. of iodized oil during bronchography. Symptoms were noted within four hours. A macular rash appeared on the second day, spread to the face and tongue, and later became vesicular. Granulomatous areas developed as the vesicles coalesced. Death occurred two weeks after the bronchography from a pneumonia following ulcerative laryngitis. Post-mortem findings revealed necrotic changes resembling polyarteritis nodosa in the gastric mucosa and bronchial tree. H.

Treatment of Migraine With Special Reference to Ergotamine Tartrate-Caffeine Rectal Suppositories. Zanfagna, P. E.: Postgrad. Med. **11**: 423, 1952.

Rectal suppositories containing 2 mg. ergotamine tartrate and 100 mg. caffeine were used in the treatment of migraine in 30 patients. When the medication was used within one hour after the onset of headache, excellent relief was experienced by 24 patients, good relief by 3, and poor relief by 3. When the suppository was inserted within two or three hours after onset of the headache, 18 had excellent results, 6 experienced good results, and 6 had no relief. The suppositories were less effective when used three hours after the onset of headache. E. W.

Allergy to the Moths of the Silk Worm. Marconi, F., Sanson, L., and Coli, S.: Accad. med., Genova **66**: 158, 1951.

A study of 100 workers in silkworm factories in Italy revealed a high incidence of cough, rhinitis, conjunctivitis, bronchial asthma, dermatitis, and angioedema. Positive reactions to cutaneous tests with the "dust" of the moths were obtained in 26 per cent of those tested and 46 per cent of this group showed a high blood eosinophilia.

The symptoms described are believed to be due to an allergic reaction to the hairs and scales of the silkworm moths. H.

Anaphylaxis

Effects of Cortisone on the Arthus Phenomenon as Related to the Time of Sensitization. A Comparison of Histopathologic Changes. Tillotson, F. W.: Arch. Path. **52**: 119, 1951.

The effects of cortisone on the Arthus phenomenon were investigated. Rabbits were given cortisone either during the period of active sensitization or immediately after this period and the results were compared.

Three groups of rabbits were sensitized to horse serum. The first group received cortisone daily during the period of active sensitization. The second group received cortisone after the period of sensitization for five days daily, just prior to the administration of the intracutaneous shocking dose. The third group received no cortisone and served as controls.

In those animals treated with cortisone during the time of active sensitization, the severity of the Arthus reaction was greatly diminished and the serum-precipitin titers were lower than those manifested by the control animals. Histologically, the control animals showed a dense infiltration of leukocytes in the dermis and subcutaneous fat and a characteristic focal acute inflammation of arterioles, venules, and capillaries with necrosis of many vessels. The animals in the cortisone-treated group showed less infiltration of leukocytes and no vascular necrosis.

In those rabbits treated with cortisone after the completion of the sensitizing injections, the skin reaction was intermediate in severity. There was little or no effect on the serum antibody titers or on vascular necrosis, but leukocyte infiltration was diminished.

The rabbits in the first group had received cortisone daily for three weeks and showed moderate atrophy of lymph nodes, thymus, bone marrow, and adrenal cortex. In the pituitary gland of these animals, the granules of the beta cells were decreased. The rabbits in the second group had received cortisone daily for five days. In these animals, there was slight to moderate atrophy of lymph nodes and thymus and minimal atrophy of the adrenal cortex. No significant changes were noted in the bone marrow or pituitary gland of the animals in the latter group. J. S.

A New Method for the Quantitative Determination of Anaphylactic Antibody in Sera of Guinea-Pigs and Rabbits. Ovary, Z.: First International Congress for Allergy, Zurich, Switzerland, Sept. 25-29, 1951.

The method is based on the permeability of the skin vessels in cutaneous local passive direct anaphylaxis of the guinea pig provoked by progressive dilutions of the serum to be dosed.

The titration is made on guinea pigs. White animals of 230 to 250 grams body weight are used. The fur of the abdomen is cut off with scissors and 0.1 ml. of the various dilutions of the serum to be examined is injected strictly intradermally. Each animal receives on each side of the abdomen one intra-

dermal injection. For the first series of experiments the following dilutions of the serum are prepared in physiological saline: concentrated, 1/10, 1/100, 1/1,000, 1/10,000, 1/50,000.

Six hours after the intradermal injections, every animal receives intravenously a mixture of 0.25 ml. of the antigen dilution (i.e., 10 mg. crystalline egg albumin in 0.25 ml. physiological saline) + 0.50 ml. of a dye (trypan blue Gruebler aqueous solution 1 per cent or Evans blue William Warner & Co. aqueous solution 0.5 per cent, or Geigy blue 536 aqueous solution 0.5 per cent). Ten minutes after the intravenous injection the animals are killed and the skin inspected particularly on the inner side, and also by transparent light. If the serum contains antibody in sufficiently high concentration, a blue spot reveals the increased permeability caused by the cutaneous direct passive anaphylaxis. In a second series of experiments, it is possible to establish the dilution which gives a just appreciable spot, the higher one giving no recognizable reaction. This limit dilution corresponds to the titer of the serum. For example, if the dilution 1/25,000 gives a barely appreciable spot, but the dilution 1/30,000 does not, the serum contains 25,000 units per 0.10 ml. of serum. For the second series of experiments, it is advisable to use 4 animals for each dilution.

This method was worked out using sera of guinea pigs and rabbits sensitized to ovalbumin. It was established that in this case one skin-sensitizing unit corresponds to 0.003 microgram antibody nitrogen.

The advantages of the method are its rapidity and simplicity, the small amount of serum needed for the determination (0.3 ml. is more than enough), as well as the sensitivity and the possibility of revealing all the biologically active antibody, even the nonprecipitating one. Author's Summary.

The Failure of Histamine to Reproduce the Arthus Phenomenon. Croxatto, O. C.: Bull. Johns Hopkins Hosp. **90**: 439, 1952.

Rabbits and guinea pigs were given intracutaneous injections of histamine in amounts varying from 2 to 47 times the calculated minimal lethal intravenous dose for an animal of comparable weight. Each animal was given just one injection. No attempt was made, in the surviving animals, to give repeated local injections to simulate the procedure usually employed in producing an Arthus reaction. Macroscopic and microscopic examination of the tissues in either the killed or sacrificed animals failed to reveal any of the typical lesions seen in the Arthus reaction. It was concluded that since a single massive intracutaneous injection of histamine does not produce an Arthus reaction, histamine is not the cause of the Arthus phenomenon. R. W.

Serum Histaminase During Rabbit Anaphylaxis. Rose, B., and Leger, J.: Proc. Soc. Exper. Biol. & Med. **79**: 379, 1952.

Rabbits were actively sensitized with egg albumin and anaphylaxis was induced from two to three weeks later by the intravenous injection of the antigen. Blood samples were taken before and about three or four minutes after the injection of the shocking dose. Blood histamine and serum histaminase determinations were made on these samples. In 18 of 19 animals, there was a significant reduction of the blood histamine and an increase in the serum histaminase levels after the induction of anaphylaxis. The one animal which failed to show these changes also failed to show signs of shock. There appeared to be no correlation between the intensity of shock and the degree of change in the blood histamine or serum histaminase values. These

observations support the hypothesis that the rapid disappearance of blood histamine which occurs during anaphylaxis in the rabbit may be due in part to activation of histaminase. B. S.

Pharmacology, Physiology, and Pathology

In Vivo Observations of the Vascular Reactions to Large Doses of Horse Serum Using the Rabbit Ear Chamber Technique. Ebert, R. H., and Wissler, R. W.: J. Lab. & Clin. Med. **38**: 497, 1951.

The effects of large doses of horse serum were observed, in vivo, using the rabbit ear chamber technique. The ears of large rabbits weighing from 3,100 to 5,400 grams were prepared and each animal was given 2 intravenous injections of sterile horse serum (10/ml./kg.) from eighteen to twenty-one days apart. Observations were made directly as well as by colored motion pictures. No immediate reaction was observed following the first intravenous injection except for a mild transitory arteriolar dilation presumably due to an increase in blood volume. Five to seven days after the first injection, vascular and intravascular changes were observed which were greatly accentuated following the second injection. The minimal and transitory localized arteriolar constrictions noted at four to seven days after the first injection were replaced by marked arteriolar dilation from two to eighteen hours after the second injection. This phase was followed by one in which more marked localized arteriolar constrictions and dilations were observed for about one week. Adherence of leukocytes to the endothelium, evidence of endothelial damage, was most marked in the larger arterioles and began seven days after the first injection. This phenomenon, which was focal, reached a maximum between twelve and twenty-four hours after the second injection and gradually declined during that week. Other evidence of arteriolar damage included endothelial swelling usually seen during the first week after the second injection. Following the second injection of horse serum, and for one or two weeks thereafter, there was marked dilation of the venules and capillaries, focal leukocyte sticking, and some swelling and proliferation of the venule endothelium. Following the sensitizing injection of horse serum, there was some slugging of the blood, but immediately after the challenging dose, there was marked agglutination of erythrocytes. Although this decreased within twelve to twenty-four hours, it increased again between the third and sixth days. Platelet and leukocyte thrombi and emboli were present in large numbers immediately after the second injection, but generally disappeared within twelve hours. Following the second injection of horse serum, diapedesis of white blood cells through the venule and arteriolar endothelium occurred. The exudate was never great nor persistent, nor was any focal necrosis of arteriolar walls observed. No reaction of any kind was observed when normal rabbit serum was substituted for horse serum at the time of the second injection.

E. W.

The Effect of Adrenocorticotropic Hormone (ACTH) Administration on Skin, Conjunctival, and Nasal Mucous Membrane Reactivity to Histamine and Antigens in Man. Grob, D., Winkenwerder, W. L., and Schoenrich, E. H.: Bull. Johns Hopkins Hosp. **90**: 301, 1952.

The effect of ACTH on dermal, conjunctival, and nasal sensitivity to histamine, d-tubocurarine, and various inhalant and bacterial antigens was studied in a group of patients most of whom had clinical pollenosis. The group also included a few cases of lupus erythematosus, intrinsic asthma, rheumatoid arthritis, and chorioretinitis. All hay fever patients were skin tested

when their symptoms were as quiescent as possible, and no individual was tested who had an actively diseased skin. Reaginic titers, as well as the generalized circulatory reaction to histamine and the local vascular phenomena following administration of intra-arterial d-tubocurarine, were also studied before, during, and after ACTH therapy. Conjunctival tests were performed by instilling drops of histamine in one eye and drops of pollen extract into the opposite eye. Nasal tests were made by insufflation from an atomizer containing either histamine or pollen antigens.

ACTH had no effect on either the localized or the generalized vascular reaction to histamine or d-tubocurarine. In the majority of patients studied, ACTH had no effect on the immediate response to skin tests with inhalant or bacterial antigens. There was, however, in almost every patient, a diminution in the amount of erythema and induration in the delayed type of skin reactions. Following cessation of ACTH therapy, there was a quick return of skin reactivity to normal. Cortisone similarly reduced delayed reactions to bacterial antigens. ACTH therapy tended to reduce conjunctival reactivity to specific antigens, but had much less effect on the histamine reaction of the conjunctival mucous membrane. There was some reduction by ACTH of nasal mucous membrane reactivity to inhalant antigens and, to a lesser degree, to histamine also. ACTH had no effect on the serum concentration of the skin-sensitizing antibody as determined by serial dilution passive transfer studies.

The above findings seem to indicate that "the therapeutic effect of ACTH in allergic hypersensitive disease is not mediated or accompanied by a general reduction in reactivity to histamine, or in the availability of such histamine-like substance as is released by d-tubocurarine." It is suggested that "ACTH may diminish the prompt reactivity to antigens or histamine of tissues that are altered by allergic disease more readily than tissues that are not so altered." R. W.

Intravenously Administered ACTH. A Preliminary Report. Renold, A. E., Forsham, P. H., Maisterrena, J., and Thorn, G. W.: New England J. Med. **244**: 796, 1951.

The activation of the adrenal cortex by ACTH administered intravenously in normal saline or in 5 per cent dextrose was studied. The fall in circulating eosinophiles and the rise in urinary 17-ketosteroid excretion served as qualitative and quantitative measures, respectively. Twenty milligrams of ACTH injected in 10 subjects over a period of one minute produced no appreciable adrenal cortical activation. The effect was increased as the infusion time was prolonged. Twenty milligrams of ACTH given over an eight-hour period produced a marked response which lasted for from sixteen to twenty hours. When this treatment was repeated daily in a subject with normal adrenal glands, the maximum response was attained in from three to eight days, after which time the degree of activation remained approximately the same. There was no response to ACTH in 5 patients with Addison's disease or in 5 patients who had undergone complete bilateral adrenalectomy for hypertension. When the infusion time was kept constant at eight hours, the adrenal cortical stimulation increased approximately linearly with the dose of ACTH up to 10 to 20 mg. Larger doses failed to increase it any further once this maximum was reached. The effect of 20 mg. ACTH given intravenously over an eight-hour period was comparable to that obtained with an amount 5 to 10 times greater injected intramuscularly in 4 doses over a twenty-four hour period. Functional involution of the adrenal cortex following prolonged cortisone therapy was overcome by ACTH more rapidly by intravenous than by intramuscular administration. Patients with rheumatoid arthritis improved some-

what earlier with intravenous ACTH therapy with approximately one-fifth to one-tenth of the intramuscular dose required. The side effects were the same with intravenous and intramuscular injections. There were no anaphylactic reactions. I. Glazer.

The Pharmacology of Ipecac. Radowski, J. L., Hagan, E. C., Fuyat, H. N., and Nelson, A. A.: J. Pharmacol. & Exper. Therap. **104**: 421, 1952.

Ipecac contains approximately 2 per cent of active alkaloids, principally emetine and cephaline. Dogs fed 10 mg./kg./day of ipecac were not affected adversely. When the dose was increased to 20 mg./kg./day, they developed anorexia, emaciation, muscular weakness, became comatose, and died within an average of thirty-eight days. At the higher dosage, a moderate to marked hypoplasia of the bone marrow was noted. "The number of mature granulocytes and erythroid cells was markedly reduced while most of the cells present were myelocytes, often atypical. Moderate liver damage was also consistently present." Other pathology consisted of myositis, focal necrosis in the adrenal cortex, and mild intestinal inflammation. Tissue analysis of cats and dogs treated with ipecac revealed that the greatest concentration of alkaloid, up to 20 per cent of the amount administered, was stored in the liver. Substantial amounts were also found in the spleen and kidney and lesser amounts in cardiac muscle. The simultaneous administration of ipecac with a large dose of barbiturate usually resulted in central nervous system depression without the appearance of ipecac's emetic effect. It was concluded that ipecac is considerably more toxic than is generally appreciated. K.

The Effect of ACTH and Cortisone on the Concentration of Circulating Diphtheria Antitoxin. Havens, W. P., Jr., Shaffer, J. M., and Hopke, C. J., Jr.; J. Immunol. **68**: 389, 1952.

After being inoculated with 50 Lf of purified diphtheria toxoid, 31 Schick-negative patients were treated for varying periods of time with either ACTH or cortisone. Many of these patients had chronic liver disease which had been confirmed by hepatic function tests and biopsies. A control group, including a large number of individuals with and without liver disease, was similarly inoculated but received no ACTH or cortisone therapy. Blood samples were obtained at intervals ranging from four hours to several days over periods varying from four to six weeks. The amount of diphtheria antitoxin in the sera was determined by titrations in the skin of rabbits. Serum protein determinations were made on each blood specimen. The findings indicated that the administration of ACTH or cortisone at various times following the injection of diphtheria toxoid did not alter the qualitative pattern of the subsequent anamnestic response when compared to the responses found in the control group. When therapy was instituted at the time antibody levels were approaching their peak range, there was, however, a more rapid decline in the antitoxic level. Large single injections of ACTH did not alter antibody titers significantly. It is concluded that administration of ACTH and cortisone did not increase the amount of circulating antibody when given during the period of decline of antibody and that they also did not prevent the production of large amounts of antibody when given early in the hyperimmunization period. R. W.

Quinidine Activity of Thephorin. Schalleck, W.: J. Pharmacol. & Exper. Therap. **105**: 291, 1952.

Auricular fibrillation was induced electrically in the anesthetized cat by direct stimulation of the auricles. Thephorin (2.5 mg./kg.) administered intravenously was more effective than quinidine (5.0 mg./kg.) in counteract-

ing fibrillation. The effects of these two drugs on the electrocardiogram of the cat were parallel, except that quinidine (10 to 20 mg./kg.) had a greater effect on the conduction rate (P-Q interval) than on the refractory period (Q-T interval), whereas Thephorin at the same dose level caused a greater lengthening of the refractory period. In the dog, acetylcholine was placed on the sinus node of the heart. This was followed by pinching of the auricle which initiated auricular fibrillation. The two drugs were administered intravenously and a "somewhat greater" hypotensive response was noted with Thephorin than with quinidine. The duration of fibrillation was reduced 56 per cent by quinidine and 76 per cent by Thephorin, using each in a dose of 2.5 mg./kg. Multiple ventricular extrasystoles were induced in dogs by the intravenous administration of epinephrine. With no treatment, the average duration of extrasystoles was sixty seconds. Increasing doses of quinidine and Thephorin progressively shortened the duration of these extrasystoles. Quinidine in a dose of 2.50 mg./kg. was 74 per cent effective and Thephorin at the same dose was 98 per cent effective in suppressing the premature contractions.

The acute toxicity of these two drugs was compared in mice, by the oral, intraperitoneal, or intravenous routes. Thephorin was found to be approximately twice as toxic as quinidine. K.

Eosinopenia Produced by ACTH in Patients With Schizophrenia. Hiatt, H. H., Rothwell, W. S., and Horwitt, M. K.: Proc. Soc. Exper. Biol. & Med. **79**: 707, 1952.

Schizophrenic patients were previously reported to demonstrate hypoadrenocorticism and this has been used as a rationale for therapy of this disorder with cortisone. The authors performed Thorn tests on 30 patients with schizophrenia of long duration. Twenty-five patients showed, on at least one occasion, a 50 per cent or greater fall in circulating eosinophiles following the injection of 25 mg. of ACTH. B. S.

Effect of Steroids Upon Resistance of Skin to Intracutaneous Injection. Winter, C. A., and Flataker, L.: Proc. Soc. Exper. Biol. & Med. **79**: 312, 1952.

The resistance offered by the skin of rats to the intracutaneous injection of fluids was measured by the amount of pressure required to perform an intracutaneous injection. A special apparatus with an automatic infusion pump was employed so that the volume of injected fluid and the rate of injection were kept constant. The resistance of the skin to injections of physiologic saline and hyaluronidase solution was compared and was found to be much lower with hyaluronidase. The animals were then injected intramuscularly with cortisone, testosterone, desoxycorticosterone, Compound S, or artisone for four days and the pressure measurements with saline and hyaluronidase were repeated. Cortisone was the only steroid which produced an effect upon the injection pressure. Cortisone increased the resistance to the injection of the saline and the hyaluronidase solution to the same extent. The effect of cortisone in increasing the resistance offered by the skin to intracutaneous injection was thus shown to be independent of the effect of the steroid upon hyaluronidase. B. S.

The Modification of Leucocytic Function in Human Windows by ACTH. Rebeick, J. W., Smith, R. W., and Margolis, R. R.: Gastroenterologia **19**: 644, 1951.

The cytology of acute inflammation was studied by a special technique which consisted of scraping a small area of skin, applying an antigen to the

denuded surface, and then placing a glass cover slip over the lesion. After thirty minutes the cover slip was removed and stained. By this process the undersurface of the cover slip becomes coated with a sample of migratory exudative cells. The antigens used in this study included egg white, diphtheria toxoid, typhoid vaccine, and old tuberculin. Investigations were made in 11 normal subjects and in 11 individuals suffering from a variety of illnesses. The entire group was studied before and during treatment with corticotrophin.

The cytology of the inflammatory exudate was studied at varying intervals up to twenty-four hours. Up to eight hours, the cell pattern was similar in both groups studied. The predominant cells were neutrophile leukocytes with only a few histiocytes present. Between eight and twelve hours, lymphocytes containing small amounts of cytoplasm appeared. During the next three hours, these cells increased in size and contained larger amounts of cytoplasm. Histiocytes were the predominant cells in the sixteen to twenty-four hour period.

During corticotrophin treatment, lymphocytes failed to appear. There was also a failure of the development of the histiocyte cell toward the end of the twenty-four hour period. Some depression of phagocytic activity was also noted. H.

Effect of Adrenocortical Steroids and Adrenocorticotropic Hormone on Electroshock Seizure Threshold. Woodbury, D. M.: J. Pharmacol. & Exper. Therap. **105**: 27, 1952.

Adult male rats were treated with cortisone, ACTH, desoxycorticosterone acetate (D.C.A.) pellets, Compound F, and several other adrenal steroids. Their electroshock seizure thresholds were then measured. The seizures were more readily induced in animals treated with cortisone acetate, Compound F acetate, and Compound A acetate, these hormones being listed in the order of decreasing effect. Compound B (corticosterone acetate) was without effect. Compound S acetate and D.C.A. elevated the seizure threshold. The administration of ACTH alone increased seizure threshold 11 per cent after twenty-eight days. Compound S did not prevent the decrease in threshold induced by cortisone. K.

The Pressor Effect of Histamine After Autonomic Ganglionic Blockade. Slater, I. H., and Dresel, P. E.: J. Pharmacol. & Exper. Therap. **105**: 101, 1952.

After autonomic blockade in cats by tetraethylammonium chloride or hexamethonium bromide, the injection of histamine induces first hypotension, then a pressor response. Dogs do not exhibit this effect. In the cats, Pyribenzamine decreased the hypotensive effect of histamine somewhat, but completely suppressed the pressor phase in the blockaded animal both before and after adrenalectomy. Atropine did not alter the pattern before or after adrenalectomy. Dibenzamine abolished the histamine pressor effect in intact and in adrenalectomized animals. Adrenalectomy alone did not affect the pressor phase of histamine. Cocaine did not alter the response of the intact animal but, in the adrenalectomized animal, abolished the pressor phase response to histamine. The possible explanations are discussed. K.

Miscellaneous

Allergy to Viral and Rickettsial Vaccine. Ratner, B., Untracht, S., and Hertzmark, F.: Am. J. Dis. Child. **83**: 608, 1952.

One hundred forty unselected children were skin tested with 3 different types of influenza-virus vaccines. The following types were tested: (1) red-

blood-cell-eluate vaccine; (2) Sharples centrifuged-type vaccine; (3) alcohol-precipitated vaccine. Nine children showed positive reactions but 6 of them also manifested positive reactions to formalin in the dilution in which it was present in the vaccines. The red-blood-cell-eluate type vaccine produced the most marked responses probably because it contained more chick embryo protein. Nineteen egg-sensitive youngsters were tested with 0.05 c.c. of a 1:5 dilution of chick-embryo-propagated mumps vaccine. The majority of these children demonstrated positive skin reactions yet no untoward reactions ensued. No mention was made as to whether the sensitivity of these subjects to egg was immunological or clinical. Skin tests performed with a vaccine containing larger quantities of egg white often produced a severe constitutional reaction in children clinically sensitive to egg. It was found, however, that most children with positive skin reactions only or mild clinical sensitivities could easily tolerate small diluted intracutaneous or subcutaneous prophylactic injections of either the mumps or the influenza vaccine when it was combined with 2 minims of epinephrine. The vaccines used in sensitive children were those which contained only minimal amounts of crude egg protein. The authors stress the need for great caution in giving chick-embryo-propagated vaccines to egg-sensitive children. If the skin test to the vaccine does not produce constitutional symptoms, vaccines of low egg protein content, when diluted and combined with epinephrine, may safely be administered to moderately egg-sensitive youngsters for prophylactic immunization.

R. W.

Clearance of Prodigiosin Dust From the Respiratory Tract of Normal and X-Irradiated Rabbits. Taplin, G. V., Grevior, J. S., Finnegan, C., and Dunn, A.: Ann. Allergy **10**: 397, 1952.

Insoluble dust particles were found to have been cleared more rapidly and effectively from the nasopharyngeal portion of the rabbit respiratory tract than from the trachea or pulmonary parenchyma. Rabbits were exposed for thirty minutes to prodigiosin dust particles ranging in size from 0.04 micra to 3.0 micra. The animals were sacrificed at regular intervals after the exposure and the amount of dust found in the various levels of the respiratory tract was measured. Significant amounts of the dust were found deep in the lung parenchyma after a single exposure. A series of rabbits which had been exposed to whole body irradiation (800 r) were subjected to the same exposure of the prodigiosin dust. In these animals, the removal of the insoluble dust particles from the respiratory tract was greatly accelerated and the efficiency of the clearance was increased over that found in normal animals.

F.

Shwartzman Phenomenon. II. Suppressive Action of HN_2 on Antigen-Antibody Provocation. Schlang, H. A.: Proc. Soc. Exper. Biol. & Med. **79**: 639, 1952.

It has been reported that the zone of hemorrhagic necrosis at the site of preparatory injection can be elicited when the usual intravenous injection of bacterial filtrate is replaced by a challenging intravenous injection of antigen into a sensitized animal (antigen-antibody reaction in vivo). Although ACTH suppresses the hemorrhagic necrosis provoked by an intravenous injection of a bacterial filtrate, it has no effect when an antigen-antibody reaction in vivo is substituted for the latter. In this study, human-serum-sensitized rabbits were treated with nitrogen mustard four days before the challenging intravenous injection of antigen. Preparatory intracutaneous injections of various bacterial filtrates were made twenty-four hours before

the challenging injection. Control animals not treated with nitrogen mustard developed a reaction of hemorrhagic necrosis in 14 out of 19 experiments. None of the 15 nitrogen-mustard-treated animals demonstrated the Shwartzman phenomenon. The effect of nitrogen mustard thus differs from ACTH in that it completely suppresses the reaction of hemorrhagic necrosis when the phenomenon is provoked by antigen-antibody reaction in vivo. B. S.

Passive Transmission of Dinitrochlorbenzene Allergy With White Blood Cells From Sensitized Guinea Pigs. Haxthausen, H.: Acta dermat.-venereol. **31**: 659, 1951.

The author successfully transferred skin hypersensitivity to dinitrochlorbenzene in normal guinea pigs by employing peritoneal exudates, containing chiefly lymphocytes, obtained from guinea pigs sensitized with dinitrochlorbenzene. Peritoneal exudates, containing chiefly granulocytes or serum from sensitized animals, failed to transfer such sensitivity. H.

Fatal P-Aminosalicylic Acid Intoxication. Muri, J.: Nord. med. **47**: 155, 1952.

A fatal reaction to para-aminosalicylic acid is reported. The outstanding clinical findings included fever, exanthem, agranulocytosis, and acute yellow atrophy of the liver. The author advises that the drug be discontinued if there is an elevation of temperature or a rash associated with its use. H.

Malignant Hypertension Following the Administration of Cortisone in Periarteritis Nodosa. Ehrenreich, T., and Olmstead, E. V.: Arch. Path. **52**: 145, 1951.

A 28-year-old man with periarteritis nodosa was treated with a short course of cortisone and soon thereafter developed fatal malignant hypertension. At autopsy, lesions of periarteritis nodosa were found in many of the organs including the kidney. These were in the acute, healing, and healed phases. Typical lesions of malignant nephrosclerosis were also found. The relationship between the administration of cortisone and the occurrence of malignant hypertension in the presence of periarteritis nodosa is discussed. J. S.

The Use of ACTH and Cortisone in Allergy. Quintero Fossas, J. M.: Alergia **5**: 1, 1951.

ACTH was used in the treatment of bronchial asthma, atopic dermatitis, and penicillin sensitivity. Cortisone was applied locally in various types of dermatitis. Patients treated with ACTH failed to show any changes in the cutaneous reactions to allergens or to histamine. The circulating antibody titer did not decrease.

Some excellent clinical responses were observed, but relapses occurred when treatment was discontinued or when the dose was reduced. The therapeutic use of these hormones should be restricted to those cases of intractable asthma and dermatitis where other therapeutic measures have failed. H.